STUDY OF THE EFFECTS OF ABNORMAL GLUCOSE TOLERANCE EXCEPTING FRANK DIABETES IN PREGNANCY IN NEWBORN.

THESIS

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DOCTOR OF MEDICINE

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C O N T E N T S

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C E R T I F I C A T E

This is to certify that work enclosed in the thesis entitled "STUDY OF THE EFFECTS OF ABNORMAL GLUCOSE TOLERANCE EXCEPTING FRANK DIABETES IN PREGNANCY IN NEWBORN" was carried out by Subhashini Gupta in our department.

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This is to certify that work enclosed in the thesis entitled "STUDY OF THE EFFECTS OF ABNORMAL GLUCOSE TOLERANCE EXCEPTING FRANK DIABETES IN PREGNANCY IN NEWBORN" is the original work carried out by Subhashini Gupta under my direct supervision and guidance in the department of Pediatrics, M.L.B. Medical College, Jhansi.

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C E R T I F I C A T E

This is to certify that the work entitled "STUDY OF THE EFFECTS OF ABNORMAL GLUCOSE TOLERANCE EXCEPTING FRANK DIABETES IN PREGNANCY IN NEWBORN", which is being submitted as a thesis for M.D.(Pediatrics) was conducted by Subhashini Gupta under my supervision & guidance. The observations recorded have been periodically checked and varified by me.

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Dated :

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Introduction

INTRODUCTION

Pregnancy is a diabetogenic state, characterized by decrease in sensitivity to insulin action at cellular level. Exact mechanism of this diminished tissue responsiveness to insulin is not completely understood but, presumably, it is due to hormonal changes of pregnancy (Fineberg et al 1983). Human placental lactogen is secreted by placental syncytiotrophoblast in increasing amount after 20 weeks gestation and is thought to be the major insulin antagonist during pregnancy. On a cellular level, insulin resistance is supposed to be due to a postreceptor mechanism (Flint DJ et al 1980). But, not all the pregnant women develop gestational diabetes, it is only 2-3 percent of all pregnancies in which gestational diabetes develop.

Normal pregnancy is characterized by fasting hypoglycemia with exaggerated glucose and insulin levels postprandially as compared to the nonpregnant state. Women, who are not able to increase the pancreatic insulin secretion to overcome pregnancy induced insulin resistance in later part of pregnancy, develop gestational diabetes.

Gestational diabetes is characterized as a state restricted to pregnant women, in whom the onset or recognition of diabetes or impaired glucose tolerance is first discovered during pregnancy.

Gestational diabetes is associated with increased perinatal mortality, it undiagnosed and/or untreated and with increased perinatal morbidity even when diagnosis is made (Donald R Coustain). Furtheremore, women with gestational diabetes are at significantly increased risk for the subsequent development of diabetes when they are not pregnant. Gestational diabetes is associated with increased maternal morbidity also. Maternal complications are UTI, hydramnios, preeclampsia, still birth etc.

Infant born to mothers with gestational diabetes are susceptible to several specific metabolic and neonatal complications as compared with normal newborn. Some of these problems are macrosomia, congenital malformations like neural tube defects, cardiovascular anomalies etc, respiratory distress syndrome polycythemia, hyperbilirubinemi hypoglycemia (Moshe Hod et al).

Recently a study by Tallarigo et al in 1986 has shown that even limited degrees of maternal hyperglycemia which are currently considered to be within normal range, i.e. two hour plasma glucose levels between 120 and 164 mg/dl may affect the outcome of pregnancy in the form of macrosomic baby. These babies are prone to have birth trauma, hypoglycemia and hyperbilirubinemia.

All these complications of impaired gestational glucose tolerance leads tc increased perinatal morbidity and mortality.

Though lots of work have been done from time to time over pregnant diabetic mothers and their infants, very little data are available on gestational diabetes and impaired gestational glucose tolerance, while only Fallerigo et al in 1986 has worked over pregnant mothers with two hour plasma glucose levels between 120 and 164 mg/dl, the levels which considered to be within normal range, and they found that these mothers had increased incidence of macrosomic babies.

This study is planned to further study the effects of abnormal gestational glucose tolerance over newborn,so that timely treatment can be given to expecting mothers and neonatal morbidity and mortality can be reduced.

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Aims of Objectives

AIMS AND OBJECTIVES

1. To detact the abnormal glucose tolerance in third trimester of pregnancy.
2. To see the effect of diet/medical therapy on mothers having abnormal glucose tolerance test.
3. To find out the glucose tolerance in mothers after termination of pregnancy.
4. To find out the effects of abnormal glucose tolerance test in mothers over newborn, eg. weight of baby, gestation of baby, congenital anomalies, RDS, hyperbilirubinemia etc.
5. To find out the blood glucose abnormalities in newborn of these mothers.
6. To find out the other metabolic changes in newborn of these mothers, eg. hypocalcemia, hyperbilirubinemia.

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Review of Literature

REVIEW OF LITERATURE

Gestational diabetes occurs in 2-3 percent of all pregnancies. Since maternal hyperglycemia leads to various maternal and neonatal complications, studies have been done from time to time to evaluate these complications.

Gestational diabetes is defined as "Carbohydrate intolerance of variable severity with onset or first recognition during pregnancy". (American Diabetes Association, 1986). Condition is associated with increased perinatal mortality, if undiagnosed or untreated and with increased perinatal morbidity, even when diagnosis is made (Donald R. Coustan).

Between 1962 to 1970 O' Sullivan et al did an analysis of perinatal mortality rate in gestational diabetes. Further analysis were made to determine the role of age and obesity in gestational diabetes, and found that gestational diabetics with age under 25 years have less incidence of pregnancy complication as compared to gestational diabetics over 25 years of age.

A study by Gabbe et al in 1977 showed that upto 25% of infants of mothers with gestational diabetes may suffer neonatal morbidity including macrosomia and birth trauma hypoglycemia, hypocalcemia and hyperbilirubinemia.

Problem statement

Prevalance of gestational diabetes :

Gestational diabetes is a heterogenous disorder with varied worldwide prevalance. In United States the prevalance of gestational diabetes is between one and three percent. An important confounding factor is obesity. Johnson and Colleagues in 1987 reported that 8 percent of 588 women who weighed more than 250 pounds had gestational diabetes compared with less than 1 percent women who weighed less than 200 pounds.

Age also is an important factor. Mestman in 1980 reported that the incidence of gestational diabetes was 3.7 percent in women younger than 20, 7.5 percent for those 20 to 30 and 13.8 percent for women older than 30.

Overall incidence of gestational diabetes is approximately 2 percent (O'Sullivan et al 1964).

Prevalance of Complication :

Moshe Hod et al in 1991 reported prevalance of fetal and perinatal complications in gestational diabetic mothers, minor congenital anomalies (19.4 to 20.5 percent), major congenital anomalies - 1.8 to 6.82 percent, hyperbilirubinemia - 8.2 to 16.7 percent, hypocalcemia - 2.7 to 5.5 percent, and polycythemia - 3.8 to 13.3 percent.

A.Y. Ranade et al in 1987 reported incidence of perinatal complications as follows. Preterm 8 percent, L.G.A. 12 percent, S.G.A. 5 percent, Birth Asphyxia 5 percent, congenital anomalies 1 percent, hypoglycemia 15 percent, hypocalcemia 4 percent, polycythemia 5 percent, hyperbilirubinemia 2 percent, cardiomyopathy 1 percent, respiratory distress 7 percent.

Physiology of Gestational diabetes :

Pregnancy is associated with major hormonal changes that readijust maternal carbohydrate metabolism. The overall effects of these changes in normal nondiabetic women are reduced fasting blood sugars and amino acid levels, but increased post prandial blood sugars, free fatty acids, ketones, triglycerides and insulin secretion in response to glucose (Phelps PL et al, 1981). Freinkel and Coworkers described these pregnancy induced metabolic changes as a state of "accelerated starvation since they resemble the metabolic response of nonpregnant women during fasting. These maternal metabolic changes help to provide a continous supply of nutrients to the developing fetus whose feeding demands are constant.

In early pregnancy (up to 20 weeks), maternal carbohydrate metabolism is affected primarily by the large

rise in estrogen and progesterone levels. Estrogen, in particular, appears to enhancle the efficacy of insulin action by stimulating Pancreatic insulin secretion and improving peripheral glucose utilization (Costrini NV et al, 1977). There is a decrease in fasting plasma glucose, improved glucose tolerance, and an increase in tissue glycogen storage.

In the latter part of pregnancy, basal insulin levels are increased, as compared to non pregnant women with comparable [redacted] plasma glucose levels (Fineberg SE et al 1983).

The mechanism of this diminished tissue responsiveness to insulin is not completely understood, but presumably relates to the hormonal changes of pregnancy. Human placental lactogen is screted by placental syncytiotrophoblast in increasing amounts after 20 weeks gestation and is thought to be the major insulin antagonist during pregnancy. (Beck P et al 1967). Elevated prolactin, cortisol and progesterone levels during pregnancy may also contribute to this process (Land grat et al 1977). On a cellular level, increased binding of insulin to adipocytes and hepatocytes in pregnant rats suggests insulin resistance is due to a postreceptor mechanism (Flint DJ et al 1971).

Thus, normal pregnancy is characterized by fasting hypoglycemia with exaggeyated glucose and insulin levels postprandially, as compared to the nonpregnant state (Phelps PL et al,) Women who are not able to augment pancreatic insulin secretion sufficiently to overcome pregnancy induced insulin resistance in the latter part of gestation, will develop excessive post prandial glucose concentration, resulting in gestional diabetes. When this insulin deficiency is severe fasting hypoglycemia also develop.

ANALYSIS OF COMPLICATIONS :

Maternal morbidity : With the advancement of pregnancy carbohydrate tolerance is decreased, several complications of pregnancy occur more commonly in diabetic women.

i) U.T.I. : There is increased incidence of UTI in diabetic women, UTI in pregnancy adversely affect the perinatal mortality (Joslin's Diabetes Mellitus).

ii) Headache : A few women develop severe headache, which require hospitalization or narcotic therapy.

iii) Pre-eclampsia : Pre-eclampsia has historically been a frequent complication of diabetic pregnancy (Joslin's diabetes mellitus).

Lauri Suhonen and Associates in 1992 reported that the frequency of both chronic hypertension and pregnancy induced hypertension and preeclampsia were higher in gestational diabetic group when compared with controls.

iv) Polyhydramnios : Polyhydramnios is more common in diabetic women and is not related to congenital malformations. There is a suspicion that hyperglycemia is related to polyhydramnios and that the better control of diabetes lessens the incidence of polyhydramnios. Premature labour precipitated by polyhydramnios is most serious complication (Joslin's Diabetes mellitus).

v) Still birth : Death of the fetus in the last weeks of pregnancy is the worst complication of diabetic pregnancy. It has also indirectly been a cause of many fetal deaths, because many women have been delivered prematurely to avoid late loss of infant. The exact cause of still birth is unknown, it appears to be metabolic, since anatomic abnormalities of the fetus & placenta are not present in every case. (Joslin's Diabetes Mellitus).

Pederson comments that 40 percent perinatal mortality results from congenital malformations. Same observations was done by Gabbe et al (1977). Joslin's Clinic has also observed a substantial incidence of congenital anomalies- 9 percent major and 5 percent minor. Among the congenital malformation highest percentage is of neural tube defects & cardiac anomalies.

ii) Fetal Macrosomia : The infants of diabetic mothers is particularly prone to macrosomia.

Moshe Hod et al reported the incidence of macrosomia as 5.6 to 25 percent in diabetic mothers.

E.Stenninger et al in 1987 in their study reported 27 percent incidence of macrosomia in infants of gestational diabetic mothers.

Tellarigo et al in 1986 has shown that even limited degrees of maternal hyperglycemia which are currently considered to be within normal range - i.e. two hour plasma glucose levels between 120 to 164 mg% may effect the outcome of pregnancy in the form of macrosomic baby. A significant correlation between the infants weight and the mother's two hour plasma glucose level was also observed.

Postulated mechanism of macrosomia is that maternal hyperglycemia results in fetal hyperglycemia and excessive stimulation of the fetal pancreas to produce insulin. There is a strong correlation of glucose levels in maternal and fetal bloodstream. Insulin facilitates the transport of nutrients like - glucose, aminoacids and free fatty acids into cells (Pederson et al).

Crawford demonstrated a maternal to fetal glucose difference of 13 mg/dl and concluded that the gradient of maternal fetal glucose concentration is maintained in a minute to minute fashion, even in the presence of rapidly changing glucose concentration in maternal blood.

Another possible mechanism is the transplacental passage of animoacids released from maternal protein stores, which stimulate the fetal islets.

Studies indicate that glucose is a less efficient stimulus to insulin release in the fetus than in adults, however, a sustained increase in fetal blood glucose concentration in utero may induce a significant rise of fetal plasma insulin level. Arginine or Leucin in the presence of glucose can markedly enhance the fetal insulin release. Since muscle tissue is quite sensitive to insuline, this offers a possible explanation for the fact that women with mild diabetes and modest

hyperglycemia sometimes deliver macrosomic infants.

Shima and associates found a strong correlation between birth weights of overgrown infants and the infant's serum insulin levels, indicating that the excessive size of certain newborns may be the result of hyperinsulinism.

Cardell found a correlation between the quantity of islets tissue at autopsy and birth weight of the ICM.

iii) Neonatal hypoglycemia : A common problem in infants of diabetic mothers is early postnatal hypoglycemia, secondary to excessive insulin secretion after division of umblical cord and the termination of placental transfer of glucose. However, the association of severe neonatal hypoglycemia with cord insulin levels has not been demonstrated in all studies.

Jonson and Bloom suggested that the neonatal pancreatic glucagon response to the postnatal fall in glucose is inappropriately small in the infants of diabetic mothers, specially in cases with sustained hypoglycemia.

E.Stenninger et al (1991) in their study observed 38 percent incidence of neonatal hypoglycemia in infants of mothers with insulin treated gestational diabetes mellitus. Hypoglycemia occurs most frequently 2 hours after birth.

Studies by Kuhl et al (1981) and Midovinik et al (1987) have shown that high maternal blood glucose concentration at delivery increases the risk of neonatal hypoglycemia.

Neonatal hypoglycemia leads to neural dysfunction. Aynstey Green et al (1987) reported acute cerebral dysfunction in newborn with blood glucose concentration less than 2.6 m mol/lit.

Another study by Lucas (1988) showed that adverse neurodevelopment outcome could be seen in children even with moderate neonatal hypoglycemia.

iv) Neonatal Pulmonary Complications : RDS is the neonatal menifestation of insufficient fetal pulmonary synthesis, storage and release of surface active phospholipids.

Driscoll et al in 1960 concluded the major cause of mortality in the infants of diabetic mothers as Respiratory Distress Syndrome.

Warren and Le Compte has confirmed those observations. Robert and Associates in their study from 1958 to 1968 found an incidence of RDS of 23 percent in infants of diabetic mothers as compared to an incidence of 13 percent in infants born to nondiabetic mothers. In this study prematurity, caesarean section without labour, intrapartum asphyxia and male sex were also associated with increased incidence of RDS, but even when these factors were controlled, incidence of RDS was 5-6 times greater in IDM as compared to infants of nondiabetic mother. The authors concluded that the metabolic abnormalities of the diabetic pregnancy itself are a cause of increased incidence of RDS.

Studies indicate that the maternal diabetic state affects fetal lung development.

Epstein and Coworker (1976) used rhesus monkey fetus, from mothers rendered hypoglycemic by the injection of streptozotocin, they observed the marked differences between the normal and hyperglycemic fetuses in the ability of lung to synthesize, store and release Lecithin, the principal component of surface active material in lung. Sosenko and Coworkers have reported in their study that hyperglycemic rabbit fetuses showed less surface active material when compared with control fetuses. Exact mechanism of this interaction has been examined in a cell culture

system by Smith and associates. They utilized a monolayer cell system of the fetal rabbit lung and examined the effect on Lecithin synthesis when insulin was added to the culture system and they found that although insulin alone results in a significant increase in Lecithin synthesis, the addition of both insulin and cortisol to cell culture results in a marked diminution of stimulatory effect observed when cortisol alone was added. Since cortisol is thought to be the physiologic stimulus for increased synthesis of Lecithin in fetal lung seen at approximately 90 percent of term gestation, they hypothesized that insulin might interfere with this normal increase in Lecithin synthesis. Therefore, the elevated insulin concentration in fetal plasma in IDM's may interfere with this sequence and leads to the increased incidence of RDS in IDMS.

v) <u>Neonatal hyperbilirubinemia & hypocalcemia</u> :

Hyperbilirubinemia was noted in 38 percent of infants of diabetic mothers studied by Pederson and 27 percent of those studied by Essex and coworkers. The cause of hyperbilirubinemia is presumed to be related to functional prematurity of hepatic enzymes necessary for conjunction of bilirubin (Osler and Coworkers 1983).

vi) Polycythemia :

Prevalance of polycythemia was reported as 3.8 - 13.3% in infants of gestational diabetics by Moshe Hod et al in 1991.

Similar observations were done by A.Y. Ranade et al in 1989. In their study they reported the prevalance of polycythemia in 10% IGDM.

According to Pedersons hypothesis, maternal hyperglycemia leads to fetal hyperinsulinemia, which inturn supresses the synthesis, storage and release of surfactant, leading to hyaline membrane disease. These pulmonary complications of diabetes leads to fetal hypoxemia, this hypoxemia stimulates haemopoietic system leading to polycythemia.

vii) Prematurity : Ranade et al in their study in 1987 has reported prematurity in 25% infants of gestational diabetics. Deodari et al in their study showed that 20% of infant born to gestational diabetic were premature.

Assessment of gestation - There are various criterias to assess the gestational age of neonate. Some are based on external characteristics, while some on neurological characteristics. But external characteristics and neurological characteristics, when taken alone are influenced by various neonatal illnesses.

EXTERNAL SIGN	SCORE				
	0	1	2	3	4
Edema	Obvious edema of hands and feet pitting over tibia	No obvious edema of hands and feet pitting over tibia	No edema		
Skin texture	Very thin. gelatinous	Thin and smooth	Smooth. Medium thickness rash of superficial peeling	Slight thickening. Superficial cracking and peeling. especially on hands and feet.	Thick and parchment-like. superficial of deep cracking.
Skin color (infact not crying)	Dark red	Uniformly pink	Pale pink. Variable over body	Pale only pink over ears, lips, palms or soles.	
Skin opacity (trunk)	Numerous veins and venules clearly seen especially over abdomen.	Veins and tributaries seen.	A few large vessels clearly seen over abdomen.	A few large vessels seen indistinctly over abdomen.	No blood vessels seen.
Lanugo (Over back)	No lanugo	Abundant. long and thick over whole back.	Hair thinning especially over lower back	Small amount of lanugo and bald areas	At least half of back devoid of lanugo
Plantar creases	No skin creases	Faint red marks over antenor hall of sole	Definite red marks over more than antenor half. Indentations over less than antenor third	Indentations over more than antenor third.	Definite deep indentations over more than antenor third
Nipple formation	Nipple barely visible. no areola	Nipple well defined areola smooth and flat. diameter <0.75 cm.	Areola stippled edge not raised. diameter <0.75 cm.	Areola stippled. edge raised. diameter >0.75 cm.	
Breast size	No breast tissue palpable	Breast tissue on one or both sides .05 cm diameters.	Breast tissue both sides one or both 0.5 to 1.0 cm.	Breast tissue both sides one or both >1 cm.	
Ear form	Pinna flat and shapeless. little or no incurving of edge.	Incurving of part of edge of pinna.	partial incurving whole or upper pinna.	Well defined incurving whole of upper pinna.	
Ear firmness	Pinna shoft easily folded no recoil.	Pinna soft easily floded slow recoil.	Cartilage to edge of pinna but soft in places ready recoil.	Pinna firm cartilage to edge instant recoil.	
Genitalia Male	Neither testis in scrotum.	At least one testis high in scrotum.	At least one testis down in scrotum.		
Female (with hips half	Labia majora widely separated. Labia	Labia majora almost cover labia minora.	Labia majora completely cover labia minora.		

Figure 1-a External characteristics of the Dubowitz examination.

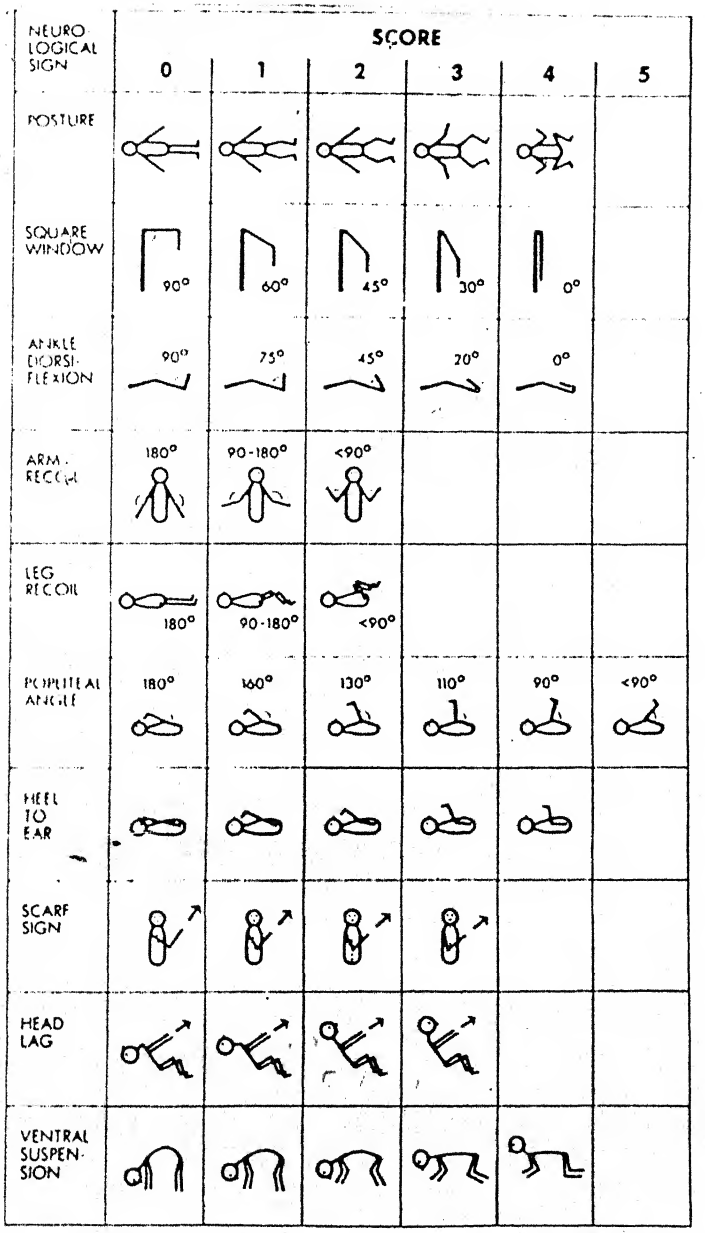

Figure 1-b Neurologic characteristics of the Dubowitz examination. Neurologic criteria are recorded and added to a final score as performed for the physical assessment. (From Dubowitz L, Dubowitz V. Gestational Age of the Newborn. Reading, MA, Addison-Wesley, 1977.)

Dubowitz has developed a method of assessment of gestational age, which include both external and neurological characteristics to minimise the influence of variable factors. This method of assessment is known as - Dubowitz's Criteria. (See fig-I).

viii) Perinatal mortality : O'Sullivan et al (1968-1970) in their study found a significantly higher ($P<0.05$) perinatal mortality rates in the gestational diabetic patients, than in normal control patients. They further determined the role of age and weight of gestational diabetic mothers over perinatal outcome and found that patients over 25 yrs. and obese have increased perinatal rates. Petit et al (1980) reported that perinatal mortality was directly proportional to the 2 hour plasma glucose level.

DIAGNOSIS OF GESTATIONAL DIABETES :

"Gestational diabetes is defined as carbohydrate intolerance of variable degree with onset or rirst recognition during pregnancy (American diabetes Association). This type of abnormal tolerance was mentioned a hundred years ago by Dancun and restated by Skipper in 1933 and White in 1935.

Subsequently, it was Jackson in 1952 and Hoet in 1954 who gave the concept of gestational diabetes as understood

today. During the past 25 years there have been many approaches to the diagnosis of gestational diabetes. The subject reviewed by Hadden in 1975 and in late 1979 at conference sponsered by American Diabetes Association, American College of Obtetrician & Gynecologists and National Institute of Health.

Risk factors for gestational diabetes : Miller and Associates in 1944 reported the quantitative relationship between histories of excessive fetal weight and increased perinatal wastage with, the later development of established diabetes.

Gilbert and Dunlop in 1949 and Moss & Mulholland in 1957 confirmed these observations. During 1950's Wilkerson initiated, classic studies of the natural history of risk factors for abnormal glucose tolerance in pregnancy. Study have been extended by O'Sullivan and Coworkers. Various risk factors for gestational diabetes are - Previous large infant, Family history of diabetes, Glycosuria, Previous perinatal deaths, obesity, abnormal obstetric history, mal-formations, hydramnios, hypertension, positive glucose challange test, hyperglycemia,prematurity, toxemia, monilia, multiparity, over-age 35,hypoglycemia.

Screening methods for glucose tolerance : Mestman and Associates conducted 3 hour OGTT with 100mg glucose.

Patients were classified in three groups - (i) those with family history of diabetes, (ii) those with obstetric history of previous large infant, perinatal loss, prematurity or toxemia in previous two or more pregnancies, and; (iii) those with no history to suggest diabetes or previous abnormal obstetric events. Upper limits of blood glucose concentrations were laid as - fasting 115 mg/dl, 1 hour 195 mg/dl, 2 hour 150 mg/dl, 3 hour 140 mg/dl. Two values above normal required for diagnosis. Following their criteria, they found the overall prevelance of abnormal glucose tolerance as 14 percent. Abnormal tolerance was most common (24%) in those with an obstetric prediabetes history, but the senstivity was low.

Macafee and Associates screened 1000 patient at 32 weeks of gestation for risk factors and conducted glucose tolerance test in all. Patients were classified in 4 groups - (i) Family history of diabetes, (ii) Age 35 (iii) Maternal obesity (90 kg) and (iv) Glycosuria. OGTT was done with 50 gms glucose with upper limits of capillary plasma as fasting 100 mg/dl, 1 hour 170 mg/dl, 2 hour 120 mg/dl and 3 hour 100 mg/dl. One abnormal value required for diagnosis.

Specificity rates were very high with all individual factors but were lower when any factor was used separately.

Guttorm, in Nerway performed OGTTs during the third trimester of pregnancy in 514 women. Risk factors were - (i) Potential diabetes (Family history of diabetes, 20% overweight or baby less than 2.5 or more than 4.5 Kg), (ii) Glycosuria, (iii) Fasting plasma glucose more than 90 mg/dl two times. Tests were done with 1gm/kg glucose lead and capillary serum was used. 2 and 2½ hour values /// 167 mg% and 145 mg% required for diagnosis.

The most extensive evaluation of risk factors for abnormal glucose tolerance in pregnancy was that reported by O'Sullivan and Associates. Glucose tolerance tests were performed on 752 pregnant women, risk factors assessed in this study included - (i) Previous delivery of infant of 4.1 kg or more; (ii) history in two or more pregnancies of perinatal death, malformations, prematurity, excessive weight gain, hypertension or proteenemia; (iii) family history of diabetes, (iv) a serum glucose level of 150 mg/dl or more 1 hour after a 50 gm glucose challange.

They concluded that positive glucose challange test was the most sensitive index of risk factors whether the test was carried out alone or in combination with other factors. The senstivity and specificity of the positive glucose challange were 79% and 87% respectively.

OGTT was performed with 100 gm glucose load, and upper limits of normal values were - fasting 105 mg/dl, 1 hour 190 gm/dl, 2 hour 165 mg/dl, and 3 hour 145 mg/dl. Two abnormal values required for diagnosis.

O'Sullivan's criteria is the most commonly used criteria for the diagnosis of gestational diabetes.

The current recommendation for detection of abnormal glucose tolerance during pregnancy were recently developed by the workshop group of American Diabetes Association, American College of Obstetrician and Gynecologists and National Institute of Health. All patient who are not known diabetics should be evalueate for risk factors, if any of these factors are present screening test is performed i.e. fasting plasma glucose level ⩾105 mg/dl or 2 hour post-prandid plasma glucose level ⩾ 120mg%. All patients with positive screening test should undergo 3-hour OGTT.

Management of Gestational Diabetes :

Gestational diabetes is defined as "Carbohydrate intolerance of variable severity with onset or first recognition during pregnancy". This condition is associated with increased perinatal mortality if undiagnosed and/or untreated, and with increased perinatal morbidity even when diagnosis is made. (American Diabetes Association).

Furthermore, women with gestational diabetes are at significantly increased risk for the subsequent development of diabetes when they are not pregnant. Thus the management of gestational diabetes is directed towards prevention of adverse effect of gestational diabetes.

At present mortality due to gestational diabetes has decreased significantly, because of early diagnosis and active management of gestational diabetes.

All the recent studies include only cases of gestational diabetes, identified and treated in some manner, whether by prescription of diet, administration of insulin, testing of fetal well being or merely by categorization as a pregnancy 'at risk' with the maintenance of increased vigilance by the health care team.

But in older studies gestational diabetes was either undiagnosed or untreated. In these studies perinatal mortality was found to be higher. Petlit et al (1980) reported that perinatal mortality rates were directly proportional to the 2-hour plasma glucose level, with values /120 mg% associated with PNM rates of 5 per 1000 and values between 160-194 mg/dl associated with rates of 44 per 1000.

O'Sullivan et al (1973) found a relative risk for perinatal mortality of 4.3 among 187 pregnancies complicated by untreated gestational diabetes compared with 259 randomly selected control pregnancies. Although in both the studies post prandial glucose was measured at each clinic visit, but no therapy was provided, as at that time no treatment goals or estimates of risk were available for gestational diabetes.

All the current studies involved some sort of intervention or intensive surveillence and thus donot represent the gestational diabetes in its undiagnosed state.

Among all the perinatal complication of gestational diabetes macrosomia is the most frequent complication.

In the study of Petit et al there was a direct relationship between 2 hour maternal plasma glucose and likelihood of birth of large baby.

In another study by Tallarigo et al (1986) similar relationship was found between 2 hour value of a 100 gm 2 hour glucose tolerance test and neonatal macrosomia.

According to Pederson hypothesis, which states that "maternal hyperglycemia is transmitted to the fetal circulation, because glucose crosses the placenta readily

fetal hyperglycemia results, causing stimulation of fetal pancreatic B cells with resulting fetal hyperinsulinemia. Because fetal insulin cannot cross the placenta to help restore normal maternal glucose levels, thus this unphysiological degree of hyperinsulinemia persist in the fetal compartment". Fetal hyperinsulinemia have been implicated in most of the adverse outcome observed in infants of diabetic mothers. Thus management of gestational diabetes is aimed at the prevention of fetal hyperinsulinemia and thus mortality and morbidity. However, prevention is not always successful therefore, another aspect of treatment of gestational diabetes is the early detection of potential morbidity and timely intervention to minimize such problem.

American College of Obstetrician & Gynecologist and American diabetes association suggest that fasting plasma glucose should be maintained below 105 mg/dl and 2 hour postpradial values below 120 mg/dl for gestational diabetic pregnancies. American diabetic association recommends that fasting and 2 hour postprandial plasma glucose should be measured at least at weekly intervals.

Gestational diabetic mothers can be managed by dietery modifications in most of cases, only 10-15 percent of gestational diabetics require insulin therapy. Oral

hypoglycemic agents must not be used in antenatal period as these drugs cross the placental bariers leading to neonatal hypoglycemia.

Dietery therapy for gestational diabetes :

The goal of dietery therapy include the avoidence of large amounts of concentrated and refined sugars which may cause rapid perturbations in circulatory glucose levels and the maintenance of consistency from day to day to allow accurate assessment of metabolic control. Adequate caloric intake is required for nourisment of developing fetus, however, excessive consumption may lead to excess weight gain exacerbating insulin resistance and raising circulatory glucose levels.

'Gabbe et al' recommends caloric requirements for gestational diabetics of 2000-2220 calories daily. meal Plan include 3 meals and a bed time snack.

If dietery therapy does not achieve adequate glycemic control, insulin therapy should be instituted.

Insulin Therapy :

If insulin is used highly purified porcaine insulin or human insulin should be administered to decrease the likelihood of antibody formation.

Although there are number of different approaches to using insulin, gestational diabetes particularly amenable is most cases to single daily injection regimes. Most individual with gestation diabetes who require insulin respond to a morning injection of a mixture of intermediate and short acting insulin. Some require a second injection before dinner, and relatively few requires an intermediate insulin dose at bed time.

O'Sullivan et al demonstrated a reduction in the likelihood of macrosomia among infants born to mothers who took prophylactic insulin prescribed without regard to maternal glycemic levels, in contrast with the offspring of gestational diabetic mothers randomized to a control group, who did not receive insulin.

Recently Oded et al in 1991 reported that insulin treatment in patients with gestational diabetes mellitus with fasting plasma glucose more than 5.3 m mol/lit significantly reduces adverse perinatal outcome.

Some authors such as O'Sullivan et al, Cowland DR and Lekin et al have advocated insulin treatment of all gestational diabetics to reduce the incidence of macrosomia.

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Material and Methods

MATERIAL & METHODS

This is a comparative study of evaluation of neonatal complications in infants of mothers having abnormal glucose tolerance and mothers having normal glucose tolerance during third trimester of pregnancy.

Study was carried out over 100 antenatal mothers in their third trimester of pregnancy attending the department of Obstetrics and Gynaecology at M.L.B. Medical College, Jhansi and infants born to these mothers. Study was done over a period of one year from June 1993 to May, 1994.

Antenatal mothers were Screened on the basis of certain factors present in history and clinical examination i.e. obesity, age, family history of diabetes, previous history of unexplained perinatal death, previous history of infant born with congenital malformations, polyhydramnios, hypertension, proteinurea and moniliasis.

These mothers underwent detailed medical history and thorough clinical examination, including obstetrical examination.

Mothers with established diabetes were excluded from the study.

Methodology :

Mothers were subjected to 100 gm glucose 3 hour glucose tolerance test, at 30 ± 2 weeks gestation, than at weekly interval, upto one week after delivery.

Criteria for abnormal glucose tolerance test :

On the basis of 3 hour GTT, mothes having abnormal glucose tolerance were grouped into three categories.

Gestational diabetes :

On the basis of O' Sullivan's criteria gestational diabetes is diagnosed, if two or more values are abnormal.

O'Sullivan's Criteria -

Fasting glucose	-	105 mg/dl
At one hour	-	190 mg/dl
At two hour	-	165 mg/dl
At three hour	-	145 mg/dl

Impaired gestational glucose tolerance :

If two hour plasma glucose levels lies between 120 to 164 mg/dl, this category is defined as impaired gestational glucose tolerance (GIGT).

Isolated abnormalities of blood glucose :

If any of the plasma glucose values exceeded the O' Sullivan's criteria at the appropriate time (IABG).

Those mothers who showed abnormal test were given suitable dietery advise and if necessary were kept on insulin. Plasma glucose values were estimated every week, so as to keep post prandial plasma glucose value below 120 mg/dl.

Newborn :

New borns of these mothers were subjected to thorough clinical examination and investigations -

Clinical examination was done to see -

- Weight of the baby at the time of birth
- Gestation of baby
- Any congenital anomaly, if present
- Any clinical evidence of respiratory distress syndrome.
- Any clinical evidence of hypocalcemia
- Hyperbilirubinemia - all the common causes of pathological jaunice were excluded.

Weight of baby :

Weight of newborn was taken by electronic weighing machine by Lectomedrik. It has got accuracy upto 10 gms. weight of the baby was plotted against intrauterine growth charts (See fig-2) and babies having birth weight more than 90th percentlie for gestational age were termed as macrogomic babies.

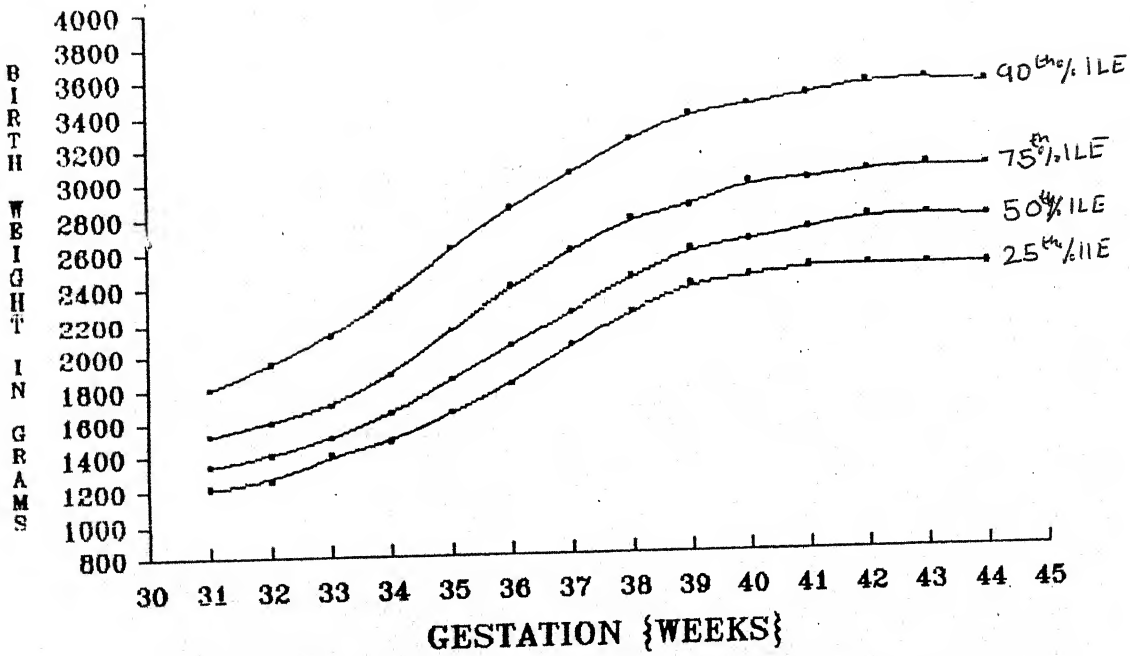

Fig 3 Intrauterine Weight chart for both sexes

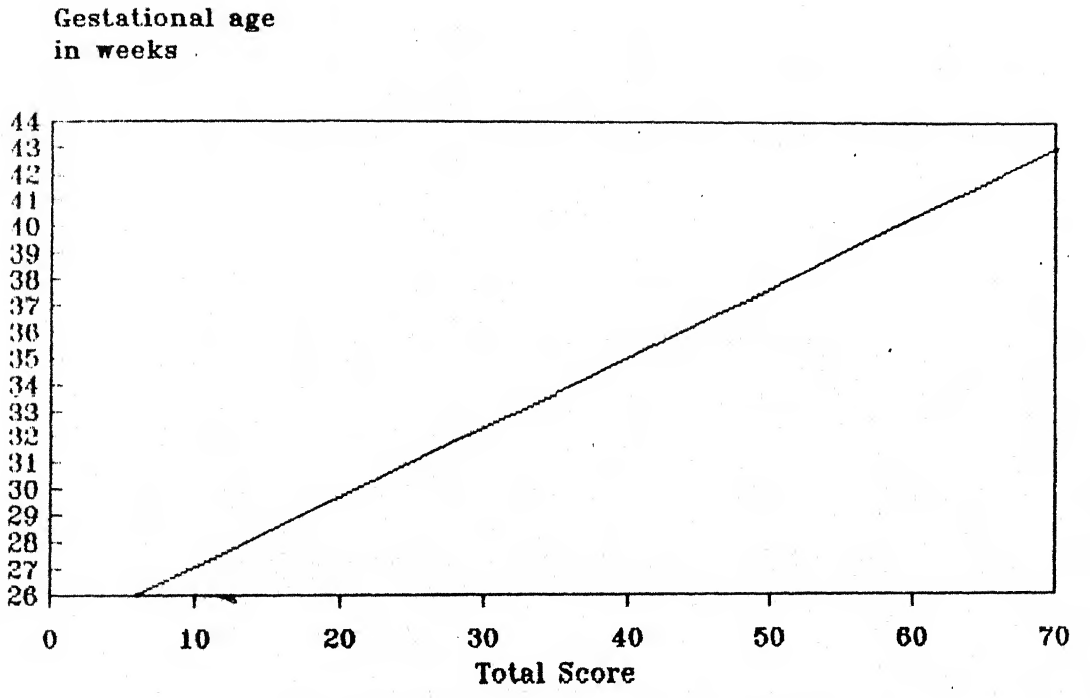

Fig-3 Both the external physical criteria score and that for the neurologic criteria are added together

Gestational age :

Gestational of baby was estimated using Dubowitz's Criteria (See fig-1

Dubowitz have derived a score based on -

(a) External characteristics

(b) Neurological characteristics. This score system is convertable into a graph (See fig - 3).

Investigations of newborn :

For the purpose of investigation blood samples of newborn was collected by heel prick method.

Investigations include -

i) Plasma glucose estimation 2 hour after birth by Hemoglukotest strips using Refloux - S glucometer.

ii) Hb estimation

iii) Serum bilirubin estimation (if clinical evidance of hyperbilirubinemia present)

(iv) Serum calcium estimation (if clinical evidence of hypocaleemia present).

Plasma glucose estimation :

Plasma glucose levels in mothers and newborns were estimated by Hemoglukotest 20-800 R. Strips using glucometer named Refloux - S supplied by Boehringer Mannheim.

Principle :

Test is based on glucose oxidase/pevoxidase reaction. Hemoglukotest strips react specifically to glucose.

Test area consists of two test zones with different sensitivity to glucose. The lower test zone gives (clearly distinguishable) colour in the range 20-120 mg/dl, and upper test zone in the range 120-800 mg/dl.

Exact values are determined with the help of Refolux - S glucometer.

Test strips were protected from humidity and direct sunlight.

Refolux - S :

It is the instrument used for plasma glucose measurement.

Principle :

The colour intensity of the reacted strip area is measured by reflectance photometry in Reflolux - S. The instrument is equipped with double beam optical system, capable of evaluating both zones of the test area simultaneously.

Technical specifications :

Type		Reflolux - S
Range of measurement	-	10-500 mg/dl
Wavelength	-	950 n.m. (infrared)
Power supply	-	6 volt battery
Storage capacity	-	Max 20 blood glucose value.

Test procedure :

- Finger was pricked with disposable needle after cleaning the test area.
- Test area of Hemoglukotest Strip 20-800 R was covered with one large drop of blood. Timer pressed immediately.
- At the long buzzer at 60 Sec. blood is wiped off with clean dry cotton.
- After 120 Sec. the display automatically shows exact plasma glucose values.

Serum bilirubin measurement :

Mitra's bilirubin reagent is used for determination of total and direct serum bilirubin.

Procedure :

Three test tubes labelled as B-blank, D-direct and T-total taken.

Reagent		For 3 ml Cuvette (m)		
		B	D	T
1. Diazo blank D reagent	-	2.0	-	-
2. Diazo working reagent	-	-	2.0	2.0
3. Serum	-	0.1	0.1	0.1
4. Reagent C	-	1.0	-	1.0
5. Distilled water	-	-	1.0	-

Contents of each tube were mixed thoroughly, after each edition.

Optical densities of contents of all the three tubes were measured at 540 $\pm$ 15 nm.

Calculation :

$$\text{Total Bilirubin} = \frac{\text{O.D. of T - O.D. of B}}{\text{O.D. of standard}} \times 5.0 \text{ mg\%}$$

$$\text{Direct bilirubin} = \frac{\text{O.D. of D - O.D. of B}}{\text{O.D. of standard}} \times 5.0 \text{ mg/dl}$$

Hemoglobin estimation :

Mitra's hemoglobin reagent was used for the purpose. Test is based on cyanmethoglobin principle.

$$\text{Calculation = gm/dl of Hb in blood} = \frac{\text{O.D. of test}}{\text{O.D. of Stand.}} \times 15$$

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Observations

OBSERVATIONS

Table - 1 : Oral glucose tolerance test in third trimester of pregnancy

OGTT Results	Cases	
	No.	%
Abnormal OGTT		
i) Gestational diabetes	14	14
ii) Isolated abnormality	12	12
iii) Impaired gestational glucose tolerance	12	12
Normal OGTT	62	62
Total	100	100

Of the total cases studied, 14 cases were having 'gestational diabetes' (i.e. two or more abnormal value of 3 hour - 100 gm GTT), 12 were having 'Isolated abnormality of plasma glucose (i.e. only one value abnormal) and 12 case were having 'impaired gestational glucose tolerance' (i.e. 2 hour plasma glucose between 120 and 164 mg/dl).

62 cases were having normal glucose tolerance test. They served as controls.

Table - 2 : Risk factors in mothers with abnormal OGTT & normal OGTT

Risk factor	Mothers with abnormal OGTT (n=38)						Mothers with normal OGTT (n=62)	
	Gestational diabetes (n= 14)		Single value abnormality (n=12)		Impaired GTT (n= 12)			
	No.	%	No.	%	No.	%	No.	%
Maternal age /25	11	78.6	8	66.6	1	8.3	29	46.7
Obesity	5	35.7	2	16.6	-	-	2	3.2
Hypertension	2	14.3	1	8.3	1	8.3	3	4.8
Oedema	1	7.1	1	8.3	1	8.3	4	6.4
Hydramnios	2	14.3	1	8.3	1	8.3	5	8.0
H/o Large baby	1	7.1	1	16.6	-	-	1	1.6
Perinatal loss	7	50.0	4	33.3	2	16.6	10	16.0
Family H/o diabetes	1	7.1	2	16.6	-	-	-	-
H/o Prematurity	2	14.3	-	-	-	-	4	6.4

Though all the risk factors were found with increased frequency in mothers with abnormal GTT, commenest factor was age over 25 yrs, this factor was present in 78.6% cases of gestational diabetes, 66.6% cases of IABG and 8.3% cases of GIGT. Second commenest factor was previous perinatal losses which was present in 50% mothers with GDM, 33.3% mothers with IABG and 16.6% mothers with GIGT, while it was present in 16%

No mother with moniliasis or history of previous congenitally malformed baby was present in either study or control group.

Table - 3 : Neonatal complications in mothers with gestational diabetes & mothers with normal GTT

Complication	Gestational diabetes mellitus (n= 14)		Normal GTT (n=62)	
	No.	%	No.	%
Macrosomia	4	28.4	3	4.69
Macrosomia with jaundice	1	07.1	-	-
Macrosomia with RDS with convulsion	1	07.1	-	-
Macrosomia with congenital malformation	-	-	-	-
Prematurity	-	-	2 (1 expired)	3.1
Prematurity with jaundice	-	-	-	-
Jaundice	-	-	5	7.7
Jaundice with hypoglycemia	1	07.1	-	-
Hypoglycemia	-	-	1	1.6
RDS	-	-	-	-
RDS with convulsion	1 (expired)	07.1	2	3.1
Congenital malformation	2 (expired)	14.2	-	-
IUD	1	07.1	2	3.1
Total	11	81.1	16	24.19

Among all the complications macrosomia was found with highest frequency as 44.4% either in isolated form or in association with other complications as compared with 4.69% in infants born to mothers with normal GTT.

Congenital malformations were found in 14.4% of infants of mothers with gestational diabetes, while no case of congenital malformations was found in infants of mothers with normal GTT. RDS was found in 14.4% infants as compared with 3.1% infants of mothers with normal GTT. Convulsions were present in 2 (14.4%) infants of GDM as compared with 3.1% infants of normal mothers, but in both the infants convulsions were present in association with other complications. Jaundice was present in 14.4% infants of GDM, as compared with 7.7% infants of mothers with normal GTT. But in both the infants of GDM jaundice was associated with other complications like macrosomia or hypoglycemia.

Though apparently all the complications seemed to occur with higher frequencies in GDM, as compared with normal, statistical significant difference $P < 0.05$ was found only with macrosomia and congenital malformations.

Overall, out of 14 infants of GDM, 11 (81.1%) had some complication, while out of 62 infants of mothers with normal GTT, only 16 (24.19% had complications. Difference was found to be statistically significant ($P < 0.05$).

Table - 4 : Neonatal complications in mothers with Isolated abnormality of blood glucose and mothers with normal GTT

Complication	Isolated abnormality of Blood glucose (n=12)		Normal GTT (n=62)	
	No.	%	No.	%
Macrosomia	2	16.6	3	4.69
Macrosomia with congenital malformation	1	08.3	-	-
Prematurity	1	08.3	2 (expired)	3.1
Prematurity with jaundice	1	08.3	-	-
Jaundice	1	08.3	5	7.7
Hypoglycemia	-	-	1	1.6
RDS with convulsion	1	08.3	2	3.1
Congenital malformation	-	-	-	-
IUD	-	-	2	3.4
Total	7	58.1	15	24.19

In infants of mothers with isolated abnormality of blood glucose also, the frequency of neonatal complications seemed to be higher, as compared with infants of mothers with normal GTT.

Macrosomia was present in 24.3% infants of IABG, as compared with 4.69% infants of mothers with normal GTT. Prematurity was present in 16.6% (2) infants of mothers having IABG in one infant prematurity was complicated by jaundice, congenital malformation was present in one infant (8.3%) and it was associated with macrosomia, RDS was present in total 8.3% infants of IABG and convulsions in 16.6% infants as compared with 3.1% and 3.1% respectively in infants born to mothers with normal GTT. Hypoglycemia did not occur in any infant of mother with IABG, while it was present in one infant (1.5%) of mother with normal GTT. Jaundice was present in 16.6% infants of IABG mothers, as compared with 7.7% infants of normal mothers.

Though all the above complications appeared to be higher in infants of mothers with isolated abnormality of blood glucose as compared with normal, statistical significant difference ($P < 0.05$) was found only with macrosomia.

Overall 7 infants (58.1%) out of 12 infants of mother with IABG had neonatal complications, as compared with 24.19% infants of mothers with normal GTT. Difference was found to be statistically significant.

Table - 5 : Neonatal complications in mothers with impaired gestational glucose tolerance and mothers having normal GTT

Complication	Impaired gestational glucose tolerance (n=12)		Normal GTT (n=62)	
	No.	%	No.	%
Macrosomia	2	16.6	3	4.69
Prematurity	1	08.3	2 (expired)	3.1
Prematurity with jaundice	1	08.3	-	-
Jaundice	1	08.3	5	7.7
Hypoglycemia	-	-	1	1.5
RDS	1	08.3	-	-
RDS with convulsion	-	-	2	3.1
Congenital malformation	-	--	-	-
IUD	-	-	2	3.1
Total	6	50.0	15	24.19

In mothers with impaired gestational glucose tolerance macrosomia, prematurity, RDS, and jaundice were found with higher frequencies, as compared with mothers having normal GTT.

Among them macrosomia was found with highest frequency (16.6%) as compared with 4.69% in normal GTT. RDS occured in 8.3% infants of mothers with GIGT, as compared with 3.1% infants of mothers having normal GTT.

Jaundice was present in total 16.6% infants of mothers having GIGT as compared with 7.7% infants of mothers having normal GTT. Prematurity was present in 16.6% infants of GIGT, and in one infant (8.3%), it was complicated by jaundice, while only 3.1% infants of normal GTT mothers were premature.

Overall out of total 12 infants born to mothers having GIGT 6 (50%) had neonatal complications, as compared with 24.19% infants of mothers having normal GTT. Difference was not statistically significant ($P > 0.05$).

Table - 6 : Relationship of maternal age with abnormal glucose tolerance & perinatal mortality

Maternal age (years)	Abnormal GTT (total no.of cases n=38)		Perinatal mortality	
	No.	%	No.	%
∠ 20	01	02.6	nil	nil
20 - 25	17	44.7	nil	nil
26 - 30	18	47.3	03	16.6
7 30	02	05.2	01	50.0
Total	38	100.0	04	-

It was found in study group i.e. mothers with abnormal OGTT, that perinatal mortality increases with advancing age of mother.

Perinatal mortality was nil in mothers less than 25 years of age, while it was 16.6% in 26 - 30 year age group and 50% in more than 30 years age group.

Table - 7 : Relationship of neonatal Hb & Plasma glucose with gestational age.

Gestational age (in weeks)	Abnormal OGGT (n=37)				Normal OGTT (n=60)			
	No.	%	Mean Hb (gm/dl)	Mean glucose (mg/dl)	No.	%	Mean Hb (mg/dl)	Mean glucose (mg/dl)
< 30	02	05.2	13	48	03	03.2	16	50.0
30 - 34	02	05.2	12	49	06	06.4	14	79.6
35 - 37	02	05.2	18	73	nil	-	-	-
> 37	31	81.5	17.6	45	51	85.0	14.6	46.7

Mean Hb of infants of mothers having abnormal GTT was 15.15 $\pm$ 2.3, and mean plasma glucose was 53.75 $\pm$ 11.2.

Mean Hb of infants of mothers having normal GTT was 14.53 $\pm$ 0.18, and mean plasma glucose was 58.16 $\pm$ 2.5.

Difference in mean Hb & mean glucose was not statistically significant ($P < 0.05$).

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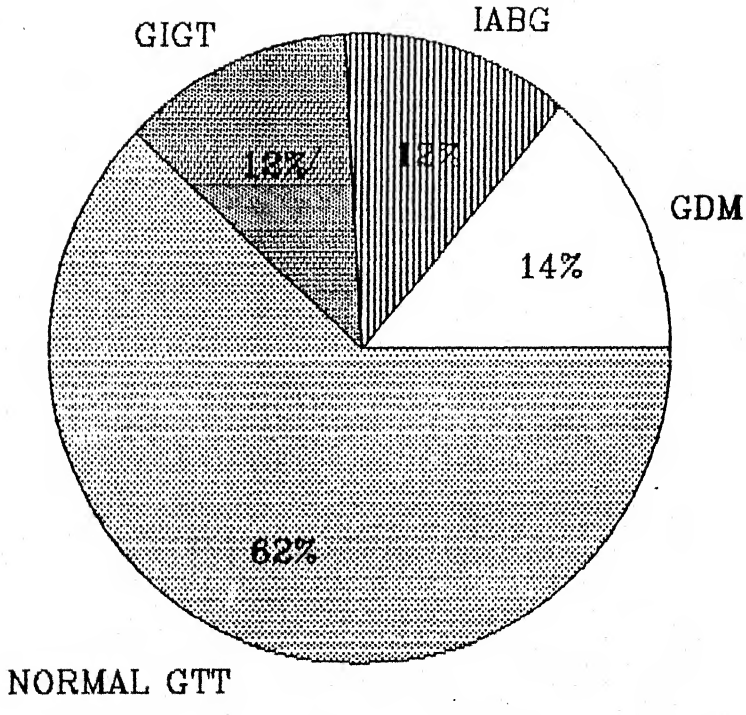
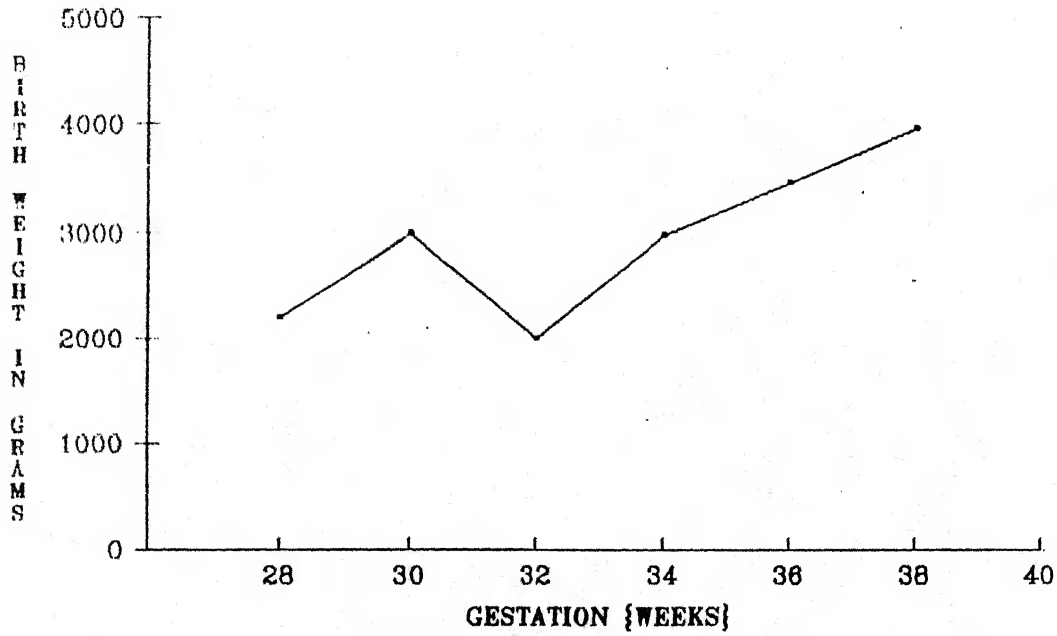
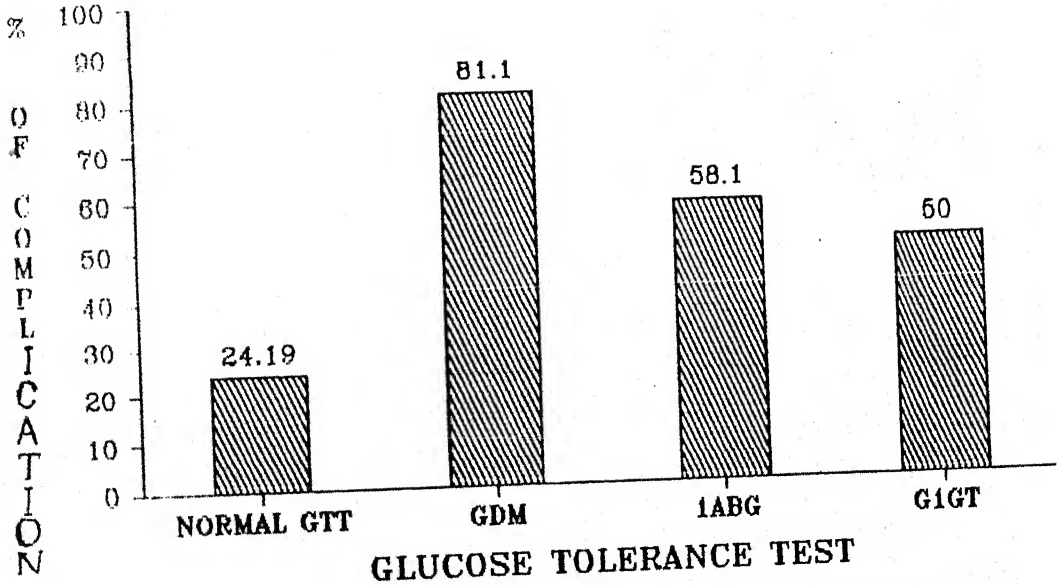


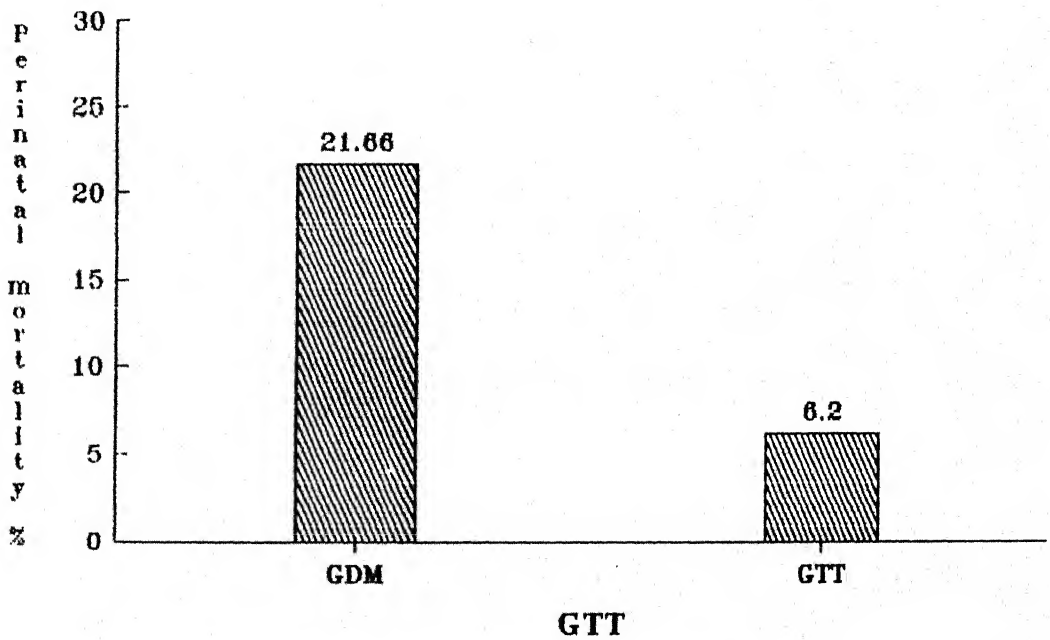
Fig–4 Showing distribution of women according to GTT



Fig–5 Mean birth weight of infants of women having abnormal glucose toleranc



Fig–6 Neonatal Complications in mothers with abnormal GTT & mothers with normal GTT



Fig–7 Showing perinatal mortality in normal GTT and GDM

Discussion

DISCUSSION

Many metabolic and hormonal changes occur in the body during pregnancy. These are the physiologic changes in response to pregnant state. Changes in the maternal carbohydrate metabolism is one of them, the overall effects of these alterations in maternal carbohydrate metabolism in normal nondiabetic woman are reduced fasting blood sugar and aminoacid levels, but increased postprandial blood sugars, free fatty acids, ketone, triglycerides and insulin secretions in response to glucose (Phelps et al). Though the insulin secretion is increased, but simultaneously body develops resistance to insulin. Women who are not able to increase the pancreatic insulin secretion sufficiently, to overcome pregnancy induced insulin resistance, develop gestational glucose intolerance.

Maternal hyperglycemia leads to various neonatal and maternal complications. Present study highlights various neonatal complications in infants born to mothers with abnormal gestational glucose tolerance.

Overall incidence of gestational diabetes is reported as approximately 2 percent (O' Sullivan et al). Deodari et al in their study reported the incidence of gestational diabetes as 55/11,920, while Tallarigo and associates in 1987 reported the incidence of impaired gestational glucose tolerance (GIGT) as 16%. In our study we found the incidenc

of GDM as 14%, and that of IABG and GIGT as 12% each. Incidence of GDM was found to be higher in our study, as compared with earlier studies, while incidence of GIGT was nearly similar to the observations by Tallarigo.

The major finding of this prospective study of infants born to mothers with abnormal gestational glucose tolerance was that macrosomia was the most frequent complication. It was found in 44.4% infants of GDM, 24.3% infants mothers with IABG and 16.6% infants of mothers with GIGT. In earlier studies Deodari and Coworkers reported 34.5% incidence of macrosomia in IGDM. E Stenninger has reported 27% incidence of macrosomia in insulin treated GDM. While Tallarigo has reported the macrosomia in 27.5% of infants born to mothers with GIGT. Our observations possess a quite similarity with previous studies. Postulated mechanism of macrosomia is that, maternal hyperglycemia results in fetal hyperglycemia and excessive stimulation of fetal pancreas to produce insulin. Insulin facilitates the transport of nutrients like glucose, aminoacids and free fatty acids into cells leading to increase in number and size of cells (Pederson et al). Arginine or Leucine in the presence of glucose can markedly enhance the fetal insulin release. With effective control of metabolic derangements in mothers, it is possible to prevent macrosomia in their babies.

Another important finding of our study was congenital malformations. We found that 2 infants (14.4%) out of 14 IGDM had major congenital malformations and one infant (8.3%) out of 12 infants of mothers with IABG had congenital malformation. Thus total 3 infants of mothers with abnormal GTT had congenital malformation, one had anencephaly, one had tracheooesophageal fistula and one had multiple small anomalies. None of the woman with normal GTT gave birth to congenitally malformed baby. This is probably because the incidence of congenital malformations in general population is very low, that of anencephaly is 1/1000 live births and tracheooesophageal fistula is 1/3000-4500 live births. Thus from the above observations it seems that incidence of congenital malformations is higher in infants born to mothers with abnormal GTT as compared with infants of mothers with normal GTT. Difference was found statistically significant ($P < 0.05$) also. A.Y. Ranade, A.K. Deodari and Tallarigo has reported a somewhat lesser incidence of congenital malformations in infants of mothers with abnormal GTT, while Joslin's clinic has reported the incidence of congenital malformations as 9% major and 5% minor in IGDM. Our observations are near to the observations by Joslin's clinic. The cause of congenital malformations is probably related to alteration in metabolic milieu in early pregnancy,

kenone bodies in combination with glucose are responsible for teratogenic effect (Joslin's diabetes clinic). For this reason good control of diabetes is essential in earliest possible weeks of pregnancy.

Increased incidence of hyperbilirubinemia is another frequent complication of diabetic pregnancies . The cause of it is presumed to be related to functional prematurity of hepatic enzymes (Osler & Coworkers). Hyperbilirubinemia was present in our study in 14.4% infants of GDM, 16.6% infants of mothers having IABG and 16.6% infants of mothers having GIGT, while jaundice was present in 7.7% infants of mothers with normal GTT. Pederson and Coworkers noted the hyperbilirubinemia in 38% infants of GDM, Similar observations was done by Essex and Coworkers. Moshe Hod et al has reported the prevalance of hyperbilirubinemia as 8.2 - 16.1%, this observation is nearly similar to our observation.

Another important cause of neonatal morbidity and mortality in infants born to mothers with abnormal GTT is respiratory distress syndrome. Epstein and Coworkers in their study concluded that maternal hyperglycemia leads to fetal hyperglycemia resulting in fetal hyperinsulinemia and this results in reduction in ability of fetal lungs to synthesize, store and release lecithin, the principal component of surface active material in lungs.

A.Y. Ranade and Associates in their study reported 7% infants with RDS in GDM, similar observations was done by Robert and Associates. Our observations was nearly similar to earlier observations, as we found RDS in 14.4% infants of GDM, 8.3% infants of mothers with IABG and 8.3% infants of mothers with GIGT, while only 3.1% infants of mothers with normal GTT had RDS. Thus the frequency of RDS seems higher with abnormal GTT as compared with normal GTT.

Prematurity was reported in 5% IGDM by A.Y. Ranade et al, while Deodari et al had reported prematurity in 20% infants of GDM. But, we did not found any case of prematurity in GDM, while 16.6% infants of IABG and 16.6% infants of GIGT were premature. Various factors like maternal hydramnios, macrosomia, placental insufficiency are incorporated in the etiology of prematurity.

A common problem in infants born to mothers with abnormal GTT is reported as early postnatal hypoglycemia, Secondary to excessive insulin secretion after division of umblical cord and termination of placental transfer of glucose. Hypoglycemia occurs most frequently 2 hours after birth (E. Stenninger et al). In our study hypoglycemia was found in 7.2% IGDM as compared with 1.5% infants of mothers with normal GTT. So the frequency of hypoglycemia appears higher in IGDM. Near similar observations was done by A.Y Ranade et al and A.K. Deodari. studies indicate that risk of

neonatal hypoglycemia increased with increasing maternal blood glucose at delivery (Kuhl et al). Thus good control of maternal hyperglycemia at term can reduce the risk of neonatal hypoglycemia.

Since very little data are available regarding neonatal complications in IABG and GIGT, we could not compare our findings with other studies except macrosomia, which was studied by Tallarigo in GIGT.

Though RDS, hypoglycemia, hyperbilirubinemia were found with higher frequencies in infants of mothers with abnormal GTT, the number of cases was small and no statistical correlation was found. We believe, it will be necessary to study a large number of cases to evaluate a possibility of a relation between abnormal gestational glucose tolerance and various neonatal complications.

Prevalance of polycythemia was reported 3.8 - 13.8% in IGDM by Moshe Hod et al, similar observations was done by A.Y. Ranade and Coworkers and A.K. Deodari. Prevalance of polycythemia (Hematocrit>65) in normal neonatal population is 1-2 percent. But in our study, we did not found any case of polycythemia in either study or control group. Though apparently mean Hb level seemed higher (15.15 gm) infants born to mothers with abnormal GTT as compared with infants born to normal GTT (Mean Hb 11.15 mg/dl). But the difference was not statistically significant.

Following advances in the management of gestational diabetes and fetal monitoring, perinatal mortality has responsibly decreased. A study conducted by Gabbe et al in 1977 showed that perinatal mortality was nearly 19/1000 in IGDM. Deodari et al reported perinatal mortality as 3.5% in IGDM. In our study perinatal mortality was 21.2% in IGDM. No mortality was found in other two categories of abnormal gestational glucose tolerance, while in normal mothers perinatal mortality was 6.2% .

Commonest cause of perinatal mortality in our study appeared to be major congenital malformations as two infants out of 3 had major congenital malformations in the form of anencephaly and tracheooesophageal fistula. This observation was similar to observations by Pederson, who showed that 40% of perinatal mortality in IGDM is due to major congenital malformations. One infant died of respiratory distress syndrome, which is another major cause of mortality in infants of diabetic mothers (Driscoll et al).

The goals of care in the management of pregnant diabetic are to acheive adequate metabolic control throughout pregnancy,

as it is known to be associated with improve perinatal outcome (Karesson et al).

Since fetal hyperinsulinemia is implicated in most of the adverse neonatal outcome, management of abnormal gestational glucose tolerance is aimed at the prevention of fetal hyperinsulinemia.

American College of Obstetrician & Gynaecologists and American diabetes association suggest that fasting plasma glucose should be maintained below 105 mg/dl and 2 hour post prandial values below 120 mg/dl for gestational diabetic pregnancies. Gestational diabetics can be managed by dietery modifications in most of cases, only 10-15 percent of gestational diabetics require insulin therapy (Ranade et al) In our study most of the antenatal mothers came at term and delivered within one or two days, so no effective treatment could be given to these mothers. Only 9 women with abnormal glucose tolerance approached before term, and they were first treated on dietery regime, but dietery therapy failed to acheive required glycemic control in four women and these women were treated with insulin therapy.

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Summary and Conclusions

SUMMARY AND CONCLUSION

Maternal hyperglycemia leads to various maternal and neonatal complications, and development of maternal hyperglycemia during antenatal period can in some cases result in development of frank diabetes mellitus subsequently.

The present study "effect of abnormal gestational glucose tolerance, excepting frank diabetes in pregnancy in newborn", highlights various neonatal complications in infants born to mothers with abnormal glucose tolerance. Mothers with preconceptional diabetes mellitus were excluded from the study.

Study was carried out over 100 antenatal women in their third trimester of pregnancy and infants born to these mothers. These antenatal women were subjected to 3 hour-100 gm glucose tolerance test. On the basis of results of OGTT, these women were categorized into 2 major groups - Normal GTT and abnormal GTT. Mothers with abnormal GTT were further classified into 3 categories - i) Gestational diabetes, ii) Isolated abnormality of blood glucose and; iii) Impaired gestational glucose tolerance.

Out of the total 100 women, 14 were having gestational diabetes, 12 had isolated abnormality blood glucose and 12 had impaired gestational glucose tolerance, while 62 women had normal GTT and they served as controls.

Mothers with abnormal GTT were subjected to 3 hour GTT at weekly interval till termination of pregnancy.

The major risk factor found with higher frequency in mothers with abnormal glucose tolerance were - previous history of perinatal loss and age over 25 years. Most of the mothers with abnormal glucose tolerance were managed with dietery modifications, only 4 required insulin therapy.

Following neonatal complications were found with higher frequencies in infants born to mothers with abnormal gestational glucose tolerance, as compared with infants of mothers with normal GTT. Macrosomia 16.6% - 44.6%, congenital malformations 0-14.4%, prematurity 0-16.6% , RDS 8.1 - 14.4%, hypoglycemia 0-7.2%, hyperbilirubinemia 14.4 - 16.6% perinatal mortality 0-21.2%. The major cause of perinatal mortality was found to be congenital malformations. The statistically significantly higher complications were only macrosomia and congenital malformations.

The following conclusions were drawn from present study -

1. Incidence of various abnormalities of blood glucose in Bundelkhand region's as follows :

   Gestational diabetes mellitus 14% ,

   Isolated abnormality of blood glucose 12%,

   Impaired gestational glucose tolerance 12%

2. Advancing maternal age and past history of perinatal loss is associated with increased risk of development of abnormal gestational glucose tolerance.

3. Neonatal complications including perinatal mortality are higher in infants born to mothers with abnormal gestational glucose tolerance, as compared with infants of mothers with normal gestational glucose tolerance.

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Appendix

APPENDIX

DEPARTMENT OF PAEDIATRICS, M.L.B. MEDICAL COLLEGE
JHANSI (U.P.)

WORKING PROFORMA

Case No.

MRD No. Dated

Mother's name

Age (years)

Baby's name

Sex

Obstetrical history

- Gravida Parity (Live, Expired) Abortion

H/O

- Previous perinatal loss — Yes No
- Birth of congenital malformed baby — Yes No

If yes, No. of losses

- Hydramnios in past pregnancy — Yes No
- Birth of large size baby — Yes No
- Hypertension in past pregnancies — Yes No
- Prematurity — Yes No
- Excessive weight gain in past or present pregnancies — Yes No
- Vulvovaginitis in past or present pregnancies — Yes No.
- Increased frequency of micturation — Yes No
- Increased thirst — Yes No
- Increased Apetite — Yes No

NATAL HISTORY

- Presentation
  - Vertex
  - Breech
  - Other
- Mode of delivery
  - Normal/Vaginal
  - Forceps
  - Caesarean

FAMILY HISTORY :
History of diabetes mellitus in family.

EXAMINATION OF MOTHER

i) General Examination

- General condition
- Height
- Weight
- Blood pressure
- Oedema
- Other

ii) Systemic Examination

a) Cardiovascular system
b) Respiratory system
c) Central nervous system

iii) Obstetrical Examination

a) At the time of admission
- Gestational age by LMP
- Abdominal girth at the level of umblicum
- Fundal height
- FHS - Rate
  - Rhythum
  - Location
- Any evidence of hydramnios

b) At term
- Abdominal girth
- Fundal height
- FHS
- Any evidence of hydramnios

Examination of Baby

I. At Birth

(A) APGAR SCORE

Colour - Pink
Blue extremities - Pink trunk
Blue

Heart rate
Respiratory rate
Response to stimuli
Muscle tone

Gestational Age

a) Last menstrual period
b) By morphological examination

Score

ii) Neurological

Score

Gestational age according to Dubowitz criteria

Anthropometric Examination

Weight
Length
Head circumference

Systemic Examination of New-born

i) Cardiovascular system
ii) Respiratory system
iii) Per Abdomen
iv) Central Nervous system

INVESTIGATIONS

Mother

3 hour glucose tolerance test

Gestation of pregnancy	Plasma glucose level			
	0 hour	One hour	Two hour	Three hour

Treatment - i) Dietary
ii) Insulin Therapy

- Baby

a) Plasma glucose level
. 2 hours after birth

b) Hb%

c) Serum calcium

d) Serum Bilirubin Direct
Indirect

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